

LETTER TO THE EDITOR

## Identifying lithium-poisoned patients who may benefit from haemodialysis remains highly challenging

Buckley et al. retrospectively assessed the need for haemodialysis based on the EXtracorporeal TRetreatments In Poisoning (EXTRIP) work-group criteria in a cohort of 361 lithium-poisoned patients.<sup>1</sup> We would like to congratulate the authors for their attempt to improve EXTRIP criteria and discuss their results in the light of our recently published study assessing EXTRIP criteria similarly in a cohort of 128 lithium-poisoned patients.<sup>2</sup> It is noteworthy that we used more stringent criteria to define severe lithium toxicity and that our patients were more severely poisoned, that is, including patients more susceptible to benefit from haemodialysis to limit the risk of fatal outcome or neurological sequelae development (Table 1).

These two studies point out the difficulties in interpreting some criteria loosely defined in the EXTRIP guideline.<sup>3</sup> The 'decreased level of consciousness' criterion was interpreted as a Glasgow coma score (GCS) of <15 in Buckley's study<sup>1</sup> but as GCS of <12 in ours.<sup>2</sup> The 'confusion' criterion was construed as onset of confusion in Buckley's study<sup>1</sup> but as GCS of 12–13 in ours.<sup>2</sup> The 'serum lithium concentration expected to be >1 mmol/L at 36 h with optimal management' criterion was determined in Buckley's study<sup>1</sup> using the  $C_t = C_0 \cdot e^{-\frac{0.161 \cdot eGFR + 6.47}{55} \cdot t}$  equation but in ours<sup>2</sup> as serum lithium concentration > 2.5 mmol/L measured 24 h after admission, taking into account the lithium half-life of ~24 h in the patient with normal

kidney function. Such discrepancies between two teams of toxicologists in translating EXTRIP criteria clearly underline the difficulties expected when non-specialist physicians will use these criteria at the bedside to target lithium-poisoned patients who could benefit from haemodialysis. Interpretation of EXTRIP criteria was more stringent in our approach than in Buckley's one. Interestingly, the use of Buckley's equation in our cohort to interpret the EXTRIP kinetic criteria would have led to perform haemodialysis in 28 additional patients in our cohort.

The development of a nomogram to predict serum lithium concentration at 36 h is an interesting proposal that clearly facilitates EXTRIP criteria application. However, we would like to raise some concerns regarding the determination and validation of the provided nomogram. The authors used the Cockroft and Gault equation with the standard male and female weights derived from the Australian population medians to estimate creatinine clearance in their patients to build the nomogram while they used the CKD-EPI formula to determine the glomerular filtration rate in the same patients to validate it. They built their equation assuming a normal volume of distribution while acute-on-chronically lithium-poisoned patients may frequently be dehydrated on admission due to vomiting and diarrhoea, and chronically lithium-poisoned patients may be either dehydrated for

**TABLE 1** Comparison of the two study cohorts of lithium-poisoned patients

	Acute on chronic poisoning		Chronic poisoning	
	Buckley's study <sup>1</sup> (N = 111)	Our study <sup>2</sup> (N = 81)	Buckley's study (N = 250)	Our study (N = 35)
Initial serum lithium (mmol/L)	2.4 (1.3–8.6)	2.8 (1.4–13.7)	1.6 (1.3–7.1)	2.8 (1.3–5.9)
Glomerular filtration rate (mL/min)	96 (16–155)	95 (13–234)	66 (5–148)	37 (6–150)
Severe toxicity <sup>a</sup>	15 (14)	32 (40)	66 (26)	11 (31)
Fatalities, N (%)	0	4 (5)	1 (0.4)	0
Actual haemodialysis, N (%)	4 (4)	17 (21)	5 (2)	3 (9)
Length of stay (day) <sup>b</sup>	1.4 (0.1–33.0)	4.0 (1–97)	4.0 (0.1–94.0)	9.0 (2–41)
Neurological sequelae on discharge, N (%)	0	12 (15)	6 (2)	13 (37)
EXTRIP criteria fulfilling, N (%) <sup>c</sup>	81 (73)	66 (81)	130 (52)	27 (77)

Note: Data are given as medians (range) or counts (%).

<sup>a</sup>Severe toxicity was defined in Buckley's study in the presence of at least one of the following criteria: coma, seizures, myoclonus, and cardiopulmonary collapse. It was defined in our study in the presence of at least one of the following conditions: seizures and/or catecholamine infusion and/or mechanical ventilation lasting >48 h.

<sup>b</sup>Patients were followed until hospital discharge in Buckley's study and until ICU discharge in our study.

<sup>c</sup>EXTRIP criteria were interpreted differently between studies.

the same reasons or presenting fluid overload in relation to acute kidney injury that has caused lithium overdose.<sup>4</sup> Finally, no information regarding patient management was provided to understand the rapidity of renal function recovery and thus clarify the reasons for failure in the prediction of serum lithium levels at 36 h.

To assess the provided nomogram from a clinical perspective, we counted the different patient outcomes compared to predicted lithium concentrations on the graphs to determine its sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV). In the acute-on-chronically lithium-poisoned patients, sensitivity was 95%, specificity 59%, NPV 96%, and PPV 46%. In the chronically lithium-poisoned patients (considering that four outcomes were missing, probably hidden by other plots, and that lithium concentrations at 36 h were not provided for the patients with neurological sequelae), sensitivity was 59%, specificity 79%, NPV 62%, and PPV 77%. Whereas Buckley et al. surprisingly concluded that their nomogram should only be used in the chronically lithium-poisoned patients, its performance appeared less good in these patients. By contrast, the elevated NPV found in the acute-on-chronically poisoned patients supported the nomogram accuracy for clinical practice in this other patient subgroup.

Considering that EXTRIP criteria require refinement, Buckley et al. proposed simplified indications for haemodialysis in lithium poisoning. The suggested criteria for acute-on-chronic lithium poisoning, based on biological parameters (i.e., renal function and lithium concentration), are quite close to ours (i.e., serum lithium >5.2 mmol/L and/or serum creatinine >200 µmol/L).<sup>2,4</sup> The haemodialysis criteria suggested for chronic lithium poisoning require a less stringent kinetic criteria but the expression of neurological toxicity manifestations. We would have been interested to know if applying these criteria to their patients would only have resulted in the additional haemodialysis of the patients who actually developed neurological sequelae.

Evidence-based EXTRIP criteria to guide haemodialysis in lithium poisoning represent an excellent basis to harmonize clinical practice. However, some criteria still require better definitions to improve their applicability and more accurately target patients at risk of fatality or neurological sequelae if not dialysed. All suggestions to outline EXTRIP criteria including Buckley's nomogram to predict if lithium will be or not >1 mmol/L at 36 h are welcome but remain to be validated using a strict methodology.<sup>5</sup>

## KEYWORDS

haemodialysis, lithium, nomogram, poisoning, renal clearance

## COMPETING INTERESTS

There are no competing interests to declare.

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